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Intraluminal HDR Brachytherapy In Palliation Of Advanced Oesophageal Cancer: Single Institution Experience.

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ABSTRACT

To do a retrospective analysis of the results of palliative HDR brachytherapy in patients with advanced esophageal cancer. Treatment records of twenty-one patients with unresectable, advanced esophageal cancer treated with palliative intent by HDR brachytherapy alone were analysed retrospectively. All patients received a total dose of 12 Gy in one fraction. Remissions of dysphagia and other clinical and radiological factors were assessed in the first month post treatment, and then in the third, sixth, and twelfth months. The survival rate was compared with some chosen clinical factors using a log-rank test and the Kaplan– Meier method. The median survival time among all patients was 5.2 months. A longer median survival time was observed when tumor size was less than 7 cm (7.2 months), longer than 7 cm (4.0 months) (logrank $p = 0.002$). Significant correlations were found between survival and the Karnofsky Performance Status, grade of dysphagia, and age. Following HDR brachytherapy for advanced esophageal cancer there was an improvement of dysphagia in most patients. The lower grade of dysphagia observed in first month post-treatment were the most important prognostic factors allowing for prolonged survival (confirmed by a multivariate analysis). In the univariate analysis, important prognostic factors for prolonged survival were: a higher Karnofsky Performance Status, and small tumor size.

Keywords: Intraluminal, brachytherapy, oesophageal cancer.

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INTRODUCTION

As few as 10–20% of esophageal cancer patients qualify for surgical treatment. Over 50% of patients with a carcinoma of the esophagus have inoperable disease at presentation due to advanced local tumor progression, metastases or a poor general condition. Most patients require palliative treatment for dysphagia. Those who do not qualify for surgery due to tumor location, as well as those with an advanced clinical stage of cancer constitute a group with poor prognosis. In the remaining 80% of patients the tumor infiltrates the outer wall of the esophagus. The probability of metastasis to the regional lymphatic nodes is proportional to the size of the tumor; it is higher than 50–60% for a tumor exceeding 5 cm (1–5). In patients with advanced cancer of the oesophagus, the poor prognosis is associated with advanced stage of the disease, reduced performance status (PS), and weight loss [6,7]. In a retrospective palliative study, the median survival was shorter for patients with WHO PS = 2 (three months) compared to patients with WHO PS 0– 1 (six months) [8]. Such patients need palliative interventions with high efficacy, short treatment duration and few side effects. Various methods of palliation including surgical bypass, laser treatment, chemotherapy, intubation, and external beam radiotherapy (EBRT) of 10–40 Gy, or a combination of the above have been used with an attempt to improve dysphagia . The prognosis continues to be dismal, with a median survival of 2.5–5 months from any of these techniques alone or a marginal improvement with a combination (9-11). A large majority of patients die due to infiltration of neighboring organs by cancer and aspiration pneumonitis. The above considerations have resulted in attempts to apply higher doses of radiation to the tumor. Endoesophageal brachytherapy makes it possible to use high doses of radiation to the tumor itself with concurrent protection of adjoining healthy tissues due to the rapid fall in the dose with the square of the distance from the center of the dose. The above treatment also leads to a smaller proportion of late radiation complications (12–16). The aim of palliative brachytherapy is to reduce dysphagia, bleeding, and to improve the patient's well-being (9, 13, 17). Due to a high mucosal dose and intratumoral necrosis, esophagobronchial fistulas are frequent complications. Recently, the risk of late complications has been shown to a large fraction dose, and combined therapy (18).

The present retrospective audit is an analysis of the effect of palliative HDR brachytherapy dysphagia relief and on survival in comparison with some chosen prognostic factors.

MATERIALS AND METHODS

Records of carcinoma esophagus treated at our centre between 2010 to 2015 were analysed . Patients who received HDR brachytherapy in combination with external beam radiotherapy for tumor recurrence after a surgical esophageal resection were excluded from the analysis . 21 patients, treated by HDR brachytherapy only, were selected for analysis. These patients had been judged to be inoperable and ineligible for external beam radiation with curative intent because of either KPS or distant spread . Prior to HDR brachytherapy, the proximal and distal ends of the tumor were identified endoscopically and a guide wire was left, over which the flexible applicator was passed down the esophagus. A median dose of 12Gy was administered with the radioactive source Iridium 192 at 1 cm from the source axis of the applicator in one fraction. The dose distributed to the surface of the tumor (5 mm from the source axis) amounted 200% of the prescribed dose. The dose administered at 12.5 mm from the source axis was 65% (at 7.5 mm from the surface of the tumor). The mean application time of the procedure was 995 ± 416 seconds (16 min 35 s, range 190–2378 s). The standard active length of application was the tumor length plus 2 cm extra at both ends of the tumor. The mean active length was 13.6 ± 2.8 cm (range 7.0–23.0 cm). For odynophagia prophylaxis Sucralfate was prescribed for a period of 4 weeks after HDR brachytherapy [19]. The extent of disease, the WHO PS, weight change, use of analgesics and selected symptoms and signs according to the NCI-CTCAE [20] were recorded at the time of inclusion, FU1 and FU2. The dysphagia was scored as follows: score 0; ability to eat a normal diet without problems, score 1; ability to eat some solid food, score 2; ability to eat semisolid food, score 3; ability to drink only, score 4; complete dysphagia [21]. Complications requiring an intervention or prolonged stay in hospital were recorded for each treatment session. Accurate dysphagia scoring on the day of the first session of HDR brachytherapy and at 6 weeks after therapy was possible in 104 patients. Complications, recurrent dysphagia and survival were analyzed for the total group of 149 patients. The results are expressed as means \pm SD; dysphagia score and survival are expressed as medians. Dysphagia scores before treatment and 6 weeks after treatment were compared with Wilcoxon signed-ranks test. Survival was analyzed with the Kaplan–Meier method.

Treatment (Radiotherapy and Oncology 37 (1995) 237–240)

A dose of 12 Gy was delivered at 1 cm distance from the central axis with a margin of 2 cm in cranial-caudal extension of the visual tumour burden. All the patients were treated with (HDR) Microselectron. In the presence of severe obstruction ILB was preceded by dilatation in 10 (47%) patients. The endoscopic findings were documented with special attention to growth pattern (exophytic, ulceration), the degree of obstruction, length of the tumour and any circumferential extension.

Response was defined as an improvement of at least one level, lasting for at least at 4-6 weeks after treatment, in order to minimize the possible effect of dilatation. Decrease of dysphagia of at least one level was defined as a relapse. Duration of response and survival was calculated from the date of treatment. Endoscopy was performed in order to confirm progression or relapse of dysphagia.

RESULTS

Response of dysphagia could be evaluated in 19 of 21 patients.

Two cases lost to follow up after treatment. Dysphagia improved in 14 of 19 evaluable patients resulting in a response rate of 67%, there was no change in 4 (13%), whereas progression was noted in 2 (20%) patients. In 5 of the 14 (35%) responders complete normalization of swallowing ability was achieved. The median duration of response was 5 months (95% CI: 4-9 months). Relapse of dysphagia occurred in 6 (37%) of the 14 patients. Sufficient palliation up to death (without any additional treatment) was achieved in 7 (44%) patients, but 4 (15%) others required one or more additional dilatations to achieve this. Additional treatment consisted of a stent in 4 (15%) patients, a second intraluminal irradiation in 4 (15%) cases, and laser treatment in 1 (5%) patients. A second treatment of brachytherapy was more frequently performed in patients who had shown an initial response. Accompanying retrosternal pain was present in 10 patients but improved in 48% of them.

Treatment itself was well tolerated, with no or very little acute toxicity. A non-fatal haematemesis occurred in one patient after an interval of 4 months, and fistulae developed in 2 in the presence of tumour.

DISCUSSION

The prognosis in patients with unresectable advanced esophageal cancer remains abysmal. The reported 2 and 5 year survival rates range from 30–40% and 10–25%, respectively, regardless of the tumor stage and treatment options (4, 12, 22–24). The prognosis is much worse in patients with stage IV and in those with inoperable advanced cancer. In recent studies, several model variations of multidisciplinary treatment have been applied to patients, such as pre-operative adjuvant or primary treatment. It must be pointed out, however, that the patients selected for those treatments without typical surgery usually have poor prognosis due to medical contraindications (e.g., fistulae), invasion of adjacent organs, and/or metastasis. The most critical aspect of this study is its retrospective investigation. However, it is difficult to carry out a randomized prospective trial comparing palliation and survival times.

Palliation of dysphagia can be achieved in majority of patients with brachytherapy alone. Brachytherapy as compared to external beam radiation therapy offers rapid tumor reduction of luminal aspect thus rapidly restoring the swallowing function and at the same time delivers relatively low dose to the surrounding normal tissues particularly lung, spinal cord and adjacent normal esophageal mucosa(25-31)(TMH PAPER).

Due to progression of the disease prior to diagnosis, dysphagia and weight loss are observed in more than 90%

HDR brachytherapy is a commonly used treatment modality for palliation of malignant dysphagia. The group of patients in this study was considered to be ineligible for a combination treatment of external beam radiation and HDR brachytherapy, due to poor general condition or metastases. Patients were predominantly treated with a single session of HDR brachytherapy of 12 Gy. In the majority of patients the procedure could be performed as a day-care procedure, which minimized hospitalization in this group of patients with a short

life expectancy. As this was a retrospective service evaluation it may be that incidence of complications is underestimated.

In our study dysphagia improved in only 53% of the patients , to be honest we were a bit disappointed with these results as dysphagia relief is a measure of good palliation. Giles Rowland and Pagliero [32], reported improvement of dysphagia occurred in 65% of the patients with HDR brachytherapy in a retrospective analysis of 40 patients (Table 3), however in a similar retrospective analysis of 197 patients by Brewster et al. [25], showed improvement of the dysphagia score occurred in 54% of 197 patients, which is comparable to our results. Was insufficient dose a cause of these disappointing results ? A study comparing compared different doses of HDR brachytherapy given in a single-fraction was done by Kulhavy et al. [33] patients received 10, 12, 15 or 18 Gy. From the results of 25 evaluable patients, they concluded that doses of 12–15 Gy were likely to give the best results in terms of relief of dysphagia with minimal morbidity. In our study all patients received 12 Gy in a single fraction. It is very well possible that a fractionated and/or higher dosage would have improved the results. This question needs further investigation. Mild esophagitis (defined as pain and increased dysphagia during the first days after treatment) was the most common side effect . Radiotherapy can also cause late radiation effects such as ulceration, fibrosis and necrosis, causing strictures in the esophagus [16, 34,35]. This occurred in 1(4%) of our patients. HDR brachytherapy in combination with laser therapy could possibly increase the effectiveness. Prior laser therapy should reduce the tumor bulk, thus both speeding up and increasing the improvement of the dysphagia score. In four non-randomized studies, laser plus HDR brachytherapy was studied prospectively and proved to be both safe and effective [1,20,23,27]. Laser plus HDR brachytherapy was compared with laser therapy alone in two prospective, randomized studies in 39 and 22 patients [21,28]. These studies showed a prolonged dysphagia-free interval after the combination of laser and HDR brachytherapy but there was no difference in survival.

CONCLUSIONS

In summary, the present data indicate that a single fraction of ILB is valuable in the palliation of dysphagia in patients with oesophageal cancer who have adverse prognostic signs. Treatment is easy to administer with little or no acute toxicity and an acceptably low complication rate. Brachytherapy provides relief of dysphagia within a few weeks. Improvement of aspects of HRQL not related to eating cannot be expected and patients should be informed thereof.

Patient Characteristics (n=21)	
Male:Female	16:5
Median Age	57.2(Range 38-72)
Distant Mets	3
Site (Upper:Middle:Lower)	5:13:3
Histology(Squamous:Adeno)	17:4

KPS	
50	4
60	15
70	3
80	2

Dyshagia Grade	
2	5
3	12
4	4

Length of infiltration	
≤7 cm	9
>7cm	12

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